EXHIBIT I

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,377	06/19/2006	Catherine J. Pachuk	051058-034000-US	3823

90162 7590 09/04/2009

David S. Resnick
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110

EXAMINER	
PENG, BO	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
09/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,377	PACHUK ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/12/09 & 3/17/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-79 and 82-97* is/are pending in the application.

4a) Of the above claim(s) *32-62,68-77 and 82-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-67,78 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/27/05;2/27/07;3/21/07;2/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *seq alignment*.

DETAILED ACTION

Restriction election

1. Applicant's election, with traverse, of Group IV and SEQ ID NOs: 3 and 10, in the reply on December 12, 2008, in acknowledged.

2. The traverse is on the ground(s) that SEQ ID NOs: 18-22 and 54-58 of Group I share substantial sequence identity to the two elected sequences. Applicants request that these sequences also be examined.

3. This argument is not persuasive. First, this application is national stage of PCT/US04/19229, filed on June 10, 2004, in which only SEQ ID NOs 1-48 was filed. The claimed SEQ ID NOs: 54-58 do not appear to be originally filed, also see Para 5 below. Secondly, SEQ ID NOs: 18-22 and 54-58 appear to have different sequences from the elected SEQ ID NOs: 3 and 10. Applicant has failed to provide a sequence comparison showing that they are substantially the same as claimed. Finally, simultaneous search and examination of multiple sequences constitutes a serous burden to the Office. Alternatively, structurally-related molecules are searched and examined using the approach of examining Applicant's preferred species first, and then genus (see MPEP 803.02). Thus, when the elected sequences are found allowable, the substantially same sequences as the elected sequence could be rejoined for examination if Applicant provides a sequence comparison showing that the additional sequences as originally filed are substantially the same as claimed. The requirement of restriction is still deemed proper, and is therefore made FINAL.

4. Accordingly, Claims 32-79 and 82-97 are pending. Claims 53-62, 68-77 and 82-97 have been withdrawn by Applicant. Claims 32-52 are withdrawn from further consideration by the

Examiner, under 37 C. F. R. 1.142(b), as being directed to a nonelected invention. Claims 63-67 and 78-79 are examined in this Office action.

Specification

New Matter

5. The amendments filed on December 12, 2005, and June 19, 2006, are objected to under 35 U.S.C. 132(a) because they introduce new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. This application is national stage of PCT/US04/19229, which contains SEQ ID NO:1-48. It is noted that Applicant submitted a new Fig. 15, and a new sequence list along with the new version of the specification on December 12, 2005, which contain an additional 28 new sequences that were not present in both PCT/US04/19229 and 60/478,076. Applicant also submitted a new version of the specification on December 12, 2005, which appears to be different from the original specification of PCT/US04/19229. A marked-up copy of the new version of the specification was not submitted alone with a clear-copy.

6. It is further noted that more new sequences were introduced by the amendment dated June 19, 2006. Applicant also failed to submit a marked-up copy of the amendment to the specification on

7. Applicant is required to **cancel any new matter,** or point to specific support in the original specification for the additions and changes in the amendment, in the reply to this Office action. Applicant is also required to submit both marked-up copy and clear copy of the amendment for review and record.

8. The use of trademarks has been noted in this application, e.g. Lipofectamine™, Opti-MEM™, Auszyme™ and Rneasy™ throughout the text. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Correction is required.

Priority

9. This application is national stage of PCT/US04/19229, filed on June 10, 2004, and claims priority over 60/478,076, filed on June 12, 2003. A review of the priority document shows support for SEQ ID NO: 3, but not SEQ ID NO: 10. Therefore, the priority date for a method of use of SEQ ID NO: 3 has been currently determined to be June 12, 2003. The priority date for a method of use of SEQ ID NO: 10, or use of both SEQ ID NOs: 3 and 10 has been currently determined to be June 10, 2004.

Information Disclosure Statement

10. The information disclosure statements submitted on December 27, 2006, February 27, 2007, March 21, 2007, and February 19, 2008, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 63 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Ill (US 5,843,770).

13. Claims 63 and 78 are directed to a composition and a method for inhibiting expression of a polynucleotide sequence of hepatitis B virus in an *in vivo* mammalian cell comprising administering to said cell a double-stranded RNA (dsRNA) effector molecule comprising an at least 19 contiguous base pair nucleotide sequence from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEO ID NO: 10, wherein U is substituted for T. The specification Para [0049] provides following definition of dsRNA effector molecule:

[0049] "By "dsRNA" is meant a nucleic acid containing a region of two or more nucleotides that are in a double stranded conformation. It is envisioned that the conserved viral sequences of the invention may be utilized in any of the many compositions known in the art or subsequently developed which act through a dsRNA-mediated gene silencing or RNAi mechanism. In various embodiments, **the dsRNA consists entirely of ribonucleotides or consists of a mixture of ribonucleotides and deoxynucleotides. ..., The dsRNA may be a single moleeule with a region of self-complementarity such that nucleotides in one segment of the molecule base pair with nucleotides in another segment of the moleeule.** In various embodiments, a dsRNA that consists of a single molecule consists entirely of ribonucleotides or includes a region of ribonucleotides that is complementary to a region of deoxyribonucleotides. Alternatively, **the dsRNA may include two different strands that have a region of complementarity to each other.** In various embodiments, both strands consist entirely of ribonucleotides, one strand consists entirely of ribonucleotides and one strand consists entirely of deoxyribonucleotides, or one or both strands contain a mixture of ribonucleotides and deoxyribonucleotides....In some embodiments, the dsRNA does not contain any single stranded regions, such as single stranded ends, or the dsRNA is a hairpin. In other embodiments, the dsRNA has one or more single stranded regions or overbangs. Desirable RNA/DNA hybrids include a DNA strand or region that is an antisense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% complementarity to a target nucleic acid) and an RNA strand or region that is a sense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% identity to a target nucleic acid). In various embodiments, the RNA/DNA hybrid is made in vitro using enzymatic or chemical synthetic methods such as those described herein or those described in WO 00/63364, filed Apr. 19, 2000. In other embodiments, a **DNA strand synthesized in vitro is complexed with an RNA strand made in vivo or in vitro before, after, or concurrent with the transformation of the DNA strand into the cell.** In yet other embodiments, **the dsRNA is a single circular nucleic acid containing a sense and an antisense region,** or the dsRNA includes a circular nucleic acid and either a second circular nucleic acid or a linear nucleic acid.

[0073]The term "in vivo" is intended to include any system wherein the cellular DNA or RNA replication machinery

is intact, including tissue culture systems, and within single cell or multicellular living organisms.

14. In view of the specification, the claimed dsRNA can be in a form of double stranded DNA, DNA/RNA hybrid, single stranded DNA or RNA. The term "in vivo" includes tissue culture systems, and within single cell or multicellular living organisms.

15. Ill teaches a method of inhibiting HBV in mice using antisense SEQ ID NO: 1 of HBV viral cis-acting post-transcriptional regulatory sequences ("PREs"), see e.g. Abstract, line 15-25, col. 2, and line 10-58, col. 11. The antisense SEQ ID NO: 1 of the prior art comprises "at least 19 contiguous base pair nucleotide sequence of the claimed dsRNA SEQ ID NO: 10, see attached sequence alignment, wherein U is substituted for T." In view of the definition of dsRNA recited above, Ill's antisense to PRE and the method of inhibiting HBV *in vivo* meet the limitation of the claims, therefore anticipates Claims 67 and 78.

16. Claims 63 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Sallberg (US20020155124, published on October 24, 2002: Now US Pat. 6,680,059).

17. Sallberg teach methods of enhancing the immune response of an animal, including humans, using HBV nucleic acid-based antigen and antiviral drug Ribavirin, wherein said nucleic acid-based antigens include a nucleotide sequence of HBV SEQ ID No: 14, see e.g. [0017] and [0041]. Sallberg also teaches that a nucleic acid-based antigen can comprise at least 9-25, 25-50, 50-100, 100-200, 200-500, 500-1000, 1000-2000, or 2000-4000 consecutive nucleotides of any one of SEQ ID NO: 14 or an RNA that corresponds to these sequences. The nucleic acid-based antigen SEQ ID NO: 14 of the prior art comprises "a double-stranded RNA

effector molecule comprising an at least 19 contiguous base pair nucleotide sequence... SEQ ID NO: 3, wherein U is substituted for T" (Claims 63 and 78), See attached sequence alignment. Sallberg teaches that HBV nucleic acid-based antigen, including SEQ ID NO:14 and its fragments, is cloned into an expression vector, see e.g. Para [0040].

18. Sallberg has inherently taught the claimed dsRNA. As defined by the specification Para [0049], the claimed dsRNA effector molecule can be in form of a double stranded DNA, DNA/RNA hybrids, or a single stranded RNA. Given that the HBV nucleic acid-based antigen comprising SEQ ID NO: 14 and its fragments of the prior art is in form of double stranded DNA, and they can form DNA/RNA hybrids, or mRNA (a single stranded RNA) *in vivo*, the HBV nucleic acid-based antigens of the prior art meet the structural limitation of the claimed dsRNA effector molecules. Thus, Sallberg's method of using the HBV nucleic acid-based antigen comprising SEQ ID NO: 14 and its fragments for inhibiting HBV *in vivo* anticipate the claimed instant Claims 63 and 78.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering the patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of their obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 63-67, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over III (US 5,843,770), Sallberg (US2002/0155124), and McCaffrey (Nature Biotechnology, 21(6):639-644; published online May 12, 2003, cited in IDS).

21. Claims 63 and 78 have been summarized *supra*. Claims 64-67 require a composition comprising two dsRNAs SEQ ID NOs: 3 and 10, and a method of inhibiting HBV *in vivo* using dsRNAs SEQ ID NOs: 3 and 10.

22. The relevance of III is set forth *supra*. In addition, III teaches that the antisense construct is an expression plasmid encoding **one** or **more** antisense transcripts (dsRNA effector molecule) which hybridize under intracellular conditions to all or a portion of a viral PRE within a viral transcript. The antisense constructs can be used to inhibit viral production, such as HBV production.

23. However, III does not teach use of two dsRNA comprises an at least 19 contiguous base pair nucleotide sequence from within SEQ ID NOs: 3 and 10.

24. The relevance of Sallberg is set forth *supra*.

25. McCaffrey teaches RNAi (dsRNA) can be applied to inhibit production of HBV replicative intermediates both in cell culture and in mice, see e. g. Abstract. Seven RNAi target sequences were chosen on the basis of their **conservation** among the major HBV genotypes. McCaffrey shows that each shRNA targets the HBV pregenomic RNA, as well as the mRNA for

the core antigen and the polymerase, and the X region and its transcript, and can inhibit HBV in cell cultures, see Fig. 2. The siRNA (dsRNA effector molecule) is encoded by the nucleic acids in the U6 shRNA expression cassette (RNA polymerase III promoters), see e.g. Fig. 1. The predicted folding of RNAi *in vivo* is shown in Fig. 1c. McCaffrey shows that RNAi effectively inhibited replication initiation in cultured cells and mammalian liver, suggesting that such an approach could be useful in the treatment of viral diseases, see e.g. Abstract.

26. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use two dsRNA comprises an at least 19 contiguous base pair nucleotide sequence from within SEQ ID NO: 3 and SEQ ID NO: 10 for inhibiting HBV *in vivo*. In the recently decided case of *KSR International Co. v. Teleflex Inc.* (82 U.S.P.Q. 2d1385, 2007), the Supreme Court provided a number of bases on which a claimed invention may be found obvious. In particular, "When there is a design need or market pressure to solve a problem and there are a finite number of identified predictable potential solutions, a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp. **If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense**".

27. In the present case, the prior art has provided a finite number of identified predictable potential solutions for the claimed method of inhibiting HBV *in vivo* using dsRNA molecules. Specifically, Ill teaches that an expression plasmid encoding one or more antisense transcripts (dsRNA effector molecule), which comprises the claimed SEQ ID NO: 10, can inhibit HBV production in mice. Sallberg teaches HBV nucleic acid-based antigen SEQ ID NO: 14, and its fragments, which comprises the claimed dsRNA effector molecule comprising SEQ ID NO: 3,

can be used for inhibiting HBV *in vivo*. McCaffrey shows that each shRNA (dsRNA) targets the HBV pregenomic RNA, the mRNA for the core antigen and the polymerase, as well as the X region and its transcript, can inhibit HBV in cell culture. McCaffrey also demonstrated that dsRNA is capable of inhibiting HBV replication in mice. Based on the prior art teachings, those of ordinary skill in the art would have had a reasonable expectation of success in using two dsRNA comprising SEQ ID NO: 3 and 10 for inhibiting HBV *in vivo*. In turn, because the claimed oligonucleotides have the properties predicted by the prior art, it would have been obvious to make such dsRNA effector molecules for inhibiting HBV *in vivo*. Therefore, the combined teachings of these references render the claimed invention obvious.

Remarks

28. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on Tu-F, 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/BO PENG/
Primary Examiner, Art Unit 1648